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NicDaeid Niamh (Orcid ID: 0000-0002-9338-0887)
McKenzie Craig (Orcid ID: 0000-0001-7244-5779)

Large-scale evaluation of ion mobility spectrometry for the rapid detection of synthetic cannabinoid receptor agonists in infused papers in prisons

Caitlyn Norman[1], Brian McKirdy[2], Gillian Walker[3], Pat Dugard[1], Niamh Nic Daéid[1], Craig McKenzie[1]

[1]Leverhulme Research Centre for Forensic Science, School of Science and Engineering, University of Dundee, UK; [2]Governor, HMP Inverness, Scottish Prison Service, Inverness, UK; [3]Public Protection Unit, Scottish Prison Service, Edinburgh, UK

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Abstract

Synthetic cannabinoid receptor agonists (SCRAs), colloquially known as "spice," are commonly used in prisons and enter establishments via the mail in the form of infused papers. Many prisons use benchtop Ion Mobility Spectroscopy (IMS) instruments to screen mail and seized materials for the presence of SCRAs and other controlled substances. The selectivity and sensitivity of Rapiscan Itemiser® 3E and Itemiser® 4DN ion trap mobility spectrometer™ (ITMS™) systems were evaluated using 21 different SCRA reference standards. Some differences in the SCRA reduced mobility (K_0) values were observed between this study and those reported previously using IMS detection systems, particularly for cumyl and quinolinyl SCRAs (e.g. 5F-PB-22, Cumyl-4CN-BINACA, and 5F-Cumyl-PEGACLONE) although this was found to have little effect at an operational level. Operational reliability of the systems was evaluated by analyzing 392 paper and card samples with known drug content. ITMS™ system results (e.g. detect or non-detect) were in agreement with gas chromatography-mass spectrometry (GC-MS) analysis in up to 95% of samples tested. Overall, this study found the ITMS™ systems tested to be effective instruments when deployed for the rapid detection of

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SCRA infused papers. Used effectively and with up to date substance libraries, they will help reduce the supply of SCRAs into prisons and identify emerging threats as they arise. Several emerging SCRAs (5F-MPP-PICA, 5F-EMB-PICA, and 4F-MDMB-BICA) were detected for the first time in Scottish prisons between May and August 2020 as a result of routine monitoring and all were detected using the ITMS™ systems tested.

1. Introduction

Drug use in prisons is one of the greatest challenges facing the criminal justice system with studies in countries throughout the world finding higher rates of lifetime drug use, injecting drug use, and problematic drug use in prisoners than in the general population[1]. However, prisons have provided a setting for some prisoners to stop their drug use. In the last decade, the emergence and wide availability of new psychoactive substances (NPS) in prisons, mainly synthetic cannabinoid receptor agonists (SCRAs), colloquially known as "spice," has made the attainment of that goal even more difficult[2].

SCRAs are a structurally diverse class of NPS[3,4], varying widely in potency and efficacy as a result of differences in their chemical structures and structural conformation[4–8]. The SCRAs available on the illicit market change regularly in response to a number of factors including the implementation of national and international legislative controls to restrict their production, prevalence, and use; the increased online availability of published research studies and patents documenting their synthesis, in vitro potency and efficacy, and biological effects; the availability of precursor materials; and, possibly, in response to an increasing understanding of their structure-activity relationships by producers and suppliers[4]. Currently, the most commonly detected SCRAs in Scottish prisons are the *tert*-leucine methyl ester derived indole- or indazole-3-carboxamide SCRAs, 5F-MDMB-PICA (5F-MDMB-2201) **(1)**, 4F-MDMB-BINACA **(2)**, and MDMB-4en-PINACA **(3)**[9]. The structures of SCRAs mentioned in the text are provided in Figure 1 and are denoted by a bold number in parentheses referring to the numbering shown in Figure 1.

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 22 European countries have reported NPS use, and particularly SCRA use, in prisons, with concerning use reported in nine countries including the UK[10]. In prisons in England and Wales, it has been estimated that 60-90% of prisoners have used SCRAs[2]. Such high prevalence has

resulted in increasing levels of disruption, violence, and crime, and has had a negative impact on prisoner safety, rehabilitation, and recovery[11-15].

In the UK, with the exception of rough-sleeping communities in England and Wales, SCRAs appear to be currently used almost exclusively in prisons, indicating that they might serve specific prison-related functions not relevant to life in the community[16,17]. A 2019 study in England, using data from interviews conducted between 2017 and 2018, found that SCRAs are replacing traditional drugs in prisons due to their perceived ease of supply as a result of their high potency, which requires smaller doses than traditional drugs, and are therefore able to be infused into paper, clothing, and other materials[17].

In order to reduce drug use by prisoners, most prisons use a combination of demand and supply reduction measures. Demand reduction measures include mandatory drug testing (MDT), now including testing for SCRAs and their metabolites, and drugs rehabilitation programs. Supply reduction measures include extra perimeter defenses, body searches, and mail scanning. Most evidence suggests that the lack of drug availability in prisons is largely responsible for the reduction in the drug use of prisoners[17], indicating that methods for the reduction of drug supply may be more effective. This is likely true for SCRAs since their easy availability in prisons is one of the most commonly stated reasons for their use[18] and is borne out, in Scotland at least, by the fact that SCRA use rarely continues once a prisoner is released[17].

SCRAs largely enter prisons via the mail system on impregnated papers or card. Within the EU, SCRA-infused letters have been reported in Finland, Germany, Hungary, Lithuania, Poland, and Sweden, as well as outside the EU in the UK[9,17,19,20]and the United States[21–23]. It was recognized several years ago that the development of new easy to use, sensitive, and specific screening methods, or re-purposing of existing technology, to detect SCRAs on mail was urgently required[20]. In some countries, prisons have adjusted their mail regulations to try to limit the supply of SCRAs[10, 24]. This has introduced some concerns about the legality of opening prisoner mail. In Scotland, according to the Prison and Young Offenders Institutions (Scotland) Rules 2011, an officer or employee of SPS may prevent mail from being received by the prisoner if it is found to contain anything deemed restricted by the Scottish Ministers[25]. Those supplying SCRAs have attempted to circumvent this security measure by disguising the infused letters as legally privileged mail, often referred to as “Rule 39” mail in England and

Wales[24] or simply as "Legal Mail" in Scotland[25], which cannot be opened or read by prison staff[24,25].

Ion mobility spectrometers (IMS) and other rapid detection devices are established tools for the screening and preliminary identification of unknown substances in a security context[26–29], particularly for the detection of trace levels of explosives and drugs within airports[30]. Analytes are introduced into the instrument on a sampling device (referred to as a sample trap) and are volatilized in a heated ionization chamber. Substances present form charged analyte ions. Ionization of neutral analytes, such as SCRAs, occurs via ion-molecule reactions to form protonated product ions, e.g. $[M+H]^+$, and may be enhanced by the presence of dopants which can suppress the ionization of non-target molecules (ammonia, nicotinamide, and ammonium carbamate are commonly used for the analysis of drugs in positive ionization mode). The ions and ion clusters formed in the ionization chamber are separated based on their behavior in an ion drift region (also known as a drift/flight tube). The rate at which ions cross the ion drift region is inversely proportional to the size, shape, and mass of the ion[31,32].

A number of different IMS instrument designs are available with a range of sample introduction interfaces, ionization sources, detectors, and proprietary compound identification algorithms being employed[29]. Most stand-alone benchtop systems use thermal desorption for sample introduction with β-particle emitting ^{63}Ni, and corona discharge (CD) ionization sources or photoionization (PI) sources using an automated calibrating UV lamp providing a stable intensity/ionization energy. There are a number of drift tube designs and in this study, Ion Trap Mobility Spectroscopy™ (ITMS™) is used. ITMS™ allows the simultaneous detection of positive and negative ions (although almost all SCRAs, and in fact most drugs, are detected in positive ion mode), and uses ion detectors based on Faraday plates[33].

IMS is one of several methods recommended by the United Nations Office on Drugs and Crime (UNODC) for the detection of SCRAs in seized materials[34]. Five studies on the detection of SCRAs using IMS instruments have been published, and to date all have used Smiths Detection IONSCAN instruments. All reported IMS to be a fast, easy to use, and highly sensitive detection method, however, only two of the studies used IMS to detect SCRAs from seized materials[34–38].

One of the limitations of IMS is that compounds with similar masses and structures cannot always be differentiated from one another[34] but operationally this is less important as such instruments are used in a presumptive/screening mode rather than in an evidential context. In fact, this can also be viewed as a benefit of the use of such systems for the detection of SCRAs. If all SCRAs behave in a similar manner in the instrument, thereby giving a similar range of drift times, the potential for false positives or for missing new SCRAs as they emerge on the illicit market is minimized. New SCRA compounds are often close analogues of compounds already on the market (e.g. **1**-**4**), so it is likely that IMS devices could still be able to detect new compounds based on the drift times and spectra of similar compounds in the library. In addition, the detection of new SCRAs appearing in prisons can be improved with the appropriate training of staff to recognize peaks that, while not alarming against a compound in the library, are within or close to the known drift time window for previously identified SCRA compounds. Samples producing such results can then be prioritized for confirmatory laboratory-based testing with more selective analytical techniques such as Gas Chromatography-Mass Spectrometry (GC-MS) and Ultra Performance Liquid Chromatography with Quadrupole Time of Flight Mass Spectrometry (UPLC-QTOF-MS).

This study evaluates the use of two ITMS™ instruments, the Rapiscan Itemiser® 3E, which uses a sealed ^{63}Ni ionization source, and the Rapiscan Itemiser® 4DN, which uses a photoionization-based source and more advance proprietary detection algorithms, for the detection of SCRAs on infused papers. The instruments were evaluated in an operationally valid manner utilizing the same substance detection libraries used by non-scientifically trained front-line staff in prison settings. To determine system selectivity, sensitivity, and adaptability to emerging drug threats, a range of SCRA reference materials representing historical SCRAs that have not been detected in Scottish prisons since large-scale SCRA monitoring started in 2018, currently prevalent SCRAs, and a number of emerging/prophetic compounds of a variety of structural classes, which might be expected to be detected in samples seized in future, were tested. In this study, 392 non-judicial paper samples seized from four Scottish prisons between June 2018 and December 2019, previously analyzed for the presence of SCRAs using GC-MS, are used as a ground truth dataset to robustly investigate the utility of IMS instruments for the screening of prison mail and other items for current and emerging SCRAs. More recently seized samples (recovered between May and August 2020) are used to assess the detection of newly emerging SCRAs.

2. Materials and Methods

2.1. Materials

Methanol and acetonitrile were HPLC grade (≥ 99.9% purity) and supplied by either Fisher Chemicals, UK or VWR Chemicals, UK.

2.2. Seized Samples

The "ground truth" samples used in this study were non-judicial or non-attributable samples seized by the Scottish Prison Service from four prisons between June 2018 and December 2019. Some samples were seized from prisoners directly, as a result of personal or cell searches, or were identified during screening of incoming mail items using the same Rapiscan Itemiser® 3E ITMS™ systems used in this study *in-situ*. Immediately after seizure, samples were placed into labelled tamperproof polythene evidence bags, sealed, and stored securely, with visually distinct papers, most likely of different origin, often being included in the same evidence bag. Once it was determined that the samples were not required for judicial proceedings, they were set aside as part of a wider SCRA monitoring study. Prior to sample uplift, items were reviewed by Scottish Prison Service staff to ensure that all personal information present on the seized materials or on the packaging was removed or redacted. Samples were uplifted by staff from the Police Scotland Drug Expert Witness Unit and transported securely to our laboratory. Samples from three of the prisons (prisons 1-3) seized between June 2018 and September 2019 have been described previously[9]. Additional samples reported in this study for the first time, detailed in the supplementary information (Table S1), include more recently seized papers from prison 1 covering samples seized between 26th September 2019 and 18th December 2019 (n=58 individual papers) and samples from an additional establishment, prison 4 (n=59), which had not previously been tested. The external packaging containing many of the seizures from prison 4 did not include seizure dates but those that did ranged from 6th May 2019 to 28th October 2019. Additional SCRA infused paper samples (n=9), seized between May and August 2020, containing emerging SCRAs not previously detected in Scottish prisons were also included in the study. Images of selected seized materials, including adapted e-cigarettes, are provided in Section 2 of the supplementary information.

The screening method is detailed in Norman, et al. (2020)[9]. In brief, samples are extracted by ultra-sonication in methanol and are qualitatively analyzed using a 7820A gas chromatograph coupled to a 5977E mass spectrometer (Agilent Technologies, Santa Clara, CA, USA). Injection mode: 1μL sample injection and used a 20:1 split into a 1mm internal diameter

deactivated glass liner pre-packed with quartz wool, injection port temperature: 200ºC, carrier gas: He, flow: 1mL/min. Column: HP-5MS, 0.33μm, 0.2 mm x 25m (Agilent Technologies). GC oven: 80ºC held for 3min; 40ºC/min to 300ºC held for 3.5 min; total run time: 12 min; transfer line: 295ºC. The mass spectrometer operated in electron ionization (EI) mode. Ionization conditions: 70eV in full scan mode (50–550 Da), ion source: 230ºC, quadrupole: 150ºC. Any substances observed within the obtained GC-MS spectra were identified by comparing their retention time and mass spectra to reference standards of known origin where available, and by comparison to NIST14, SWGDRUG (v3.5), and Cayman Chemicals (versions v04262019, v09112019 and v09222020) mass spectral libraries with a minimum acceptable reverse match value of 850. Orthogonal confirmatory analysis was carried out using a Xevo Ultra Pressure Liquid Chromatography-Photodiode Array-Quadrupole Time of Flight-Mass Spectrometer (UPLC-PDA-QToF-MS; Waters Corporation, Milford, MA, USA). The methanol extracts used for GC-MS analysis were diluted 100-fold in 50:50 ultrapure water/acetonitrile prior to analysis. Mobile phases used were (A) LC-MS grade water with 0.1 % formic acid (V/V %) and (B) acetonitrile with 0.1 % formic acid (V/V %). The gradient used was 50:50 A:B from 0.0-4.0 min, 25:75 A:B from 4.0-5.0 min, 5:95 A:B from 5.0-5.99 min and 50:50 A:B from 6.0-7.0 min. Flow rate was 0.5 mL/min and 1 μL of sample was injected onto an ethylene bridged hybrid (BEH) C_{18} column (50 × 2.1 mm, 1.7 μm particle size; Waters Corporation, Milford, MA, USA). The QToF was operated in positive ionization mode with a source temperature of 120 ºC, a desolvation temperature at 500 ºC and a capillary voltage at 2.25 kV. ToF-MS analysis for the high-resolution determination of molecular mass was carried out with a collision energy at 6 V, with a scan range of 100-1000 Da. Mass error of the measured accurate mass from theoretical monoisotopic mass was required to be <10ppm and the UV spectra were compared with reference standards of known origin, where available. MS/MS spectra were obtained from selected parent ion fragmentation using collision energies between 10 and 30 V for further structural confirmation (scan range 100-500 Da). The GC-MS and UPLC-PDA-QToF-MS results for many of the samples provided in this study have been reported previously[9]. Sample details, GC-MS and UPLC-PDA-QToF-MS data from samples not previously reported are provided in the supplementary information (Table S1). ITMS™ data for all samples analyzed in this study are provided in in the supplementary information (Tables S6.1 and S6.2).

2.3. Reference Standards

Cumyl-4CN-BINACA **(5)**, 5F-Cumyl-PEGACLONE **(7)**, (*S*)-ADB-FUBINACA **(8)**, PB-22 (QUPIC) **(9)**, FUB-PB-22 **(10)**, (*S*)-5F-ADB-PINACA **(11)**, (*S*)-5F-AMB-PINACA (5F-AMB) **(12)**, and (*S*)-ADB-CHMINACA (MAB-CHMINACA) **(13)** reference standards were obtained from Chiron, Trondheim, Norway as 1 mg/mL solutions in methanol. Reference standards for (*S*)-5F-MDMB-PICA **(1)** (>98.7% purity); (*S*)-4F-MDMB-BINACA **(2)** (99.7% purity); (*S*)-MDMB-4en-PINACA (5-cl-adb-a) **(3)** (98.6% purity); (*S*)-5F-MDMB-PINACA **(4)** (99.6% purity); (*S*)-AMB-CHMICA (MMB-CHMICA) **(6)** (99.6% purity); (*S*)-AB-CHMINACA **(14)** (>99% purity); (*S*)-AMB-FUBINACA (MMB-FUBINACA, FUB-AMB) **(15)** (>98% purity); (*S*)-AMB-4en-PICA (MMB-022, MMB-4en-PICA) **(16)** (99.7% purity); (*S*)-MDMB-4en-PICA **(17)** (>99.7% purity); (*S*)-MDMB-FUBINACA **(18)** (>99.9% purity); and (*S*)-AB-FUBINACA **(19)** (99% purity) were obtained via in-house synthesis as detailed previously[5,39]. 5F-PB-22 (5F-QUPIC) **(20)** (99% purity) and (*S*)-MDMB-CHMICA **(21)** (99% purity) were synthesized and supplied by the Sutcliffe Group at Manchester Metropolitan University, Manchester, UK. All reference standards were analyzed by GC-MS prior to ITMS™ testing.

2.4. ITMS™ Testing Procedure

Three Itemiser® 3E (Rapiscan Systems Limited, Surrey, UK) and one Itemiser® 4DN (Rapiscan System Limited, Surrey, UK) were used during the study. Both models are ion trap mobility spectrometers (ITMS™). While the overall mechanism of detection is the same as IMS, ITMS™ does not have a shutter grid, but instead pulses the ions from a field free ionization chamber into the drift tube where the ions are guided to the detector by an electric field. Removing the shutter grid, commonly used in other instruments, is reported to eliminate the associated loss of ions and can improve sensitivity[33]. The Itemiser® 4DN uses a photoionization source with an auto calibrating UV lamp whereas the Itemiser® 3E uses chemical ionization with a radioactive ^{63}Ni source. The "narcotics" factory operating method was used with a detector temperature of over 200ºC and desorber temperature of 235ºC. For each sample, the 4DN produces multiple datasets, denoted Region 0 and Region 1, for proprietary algorithm evaluation.

The instruments were received loaded with the drug reference library supplied and maintained by the instrument manufacturer, tailored to the prison drug detection market. These libraries

are updated at regular intervals as new, relevant, compounds are identified in monitoring programmes. The current library, as used in this study, provides identification data and system alarm criteria for nine SCRA compounds ("spice" alarms) known to previously have been or to be currently circulating in UK prisons. The "spice" alarms are derived from the analytical data produced by the instrument manufacturer. The alarm criteria differ from one another in terms of the SCRA drift time calculated from the mean of multiple analyses within and between instruments across a range of concentrations, the width (in ms) of the detection windows, and alarm peak thresholds related to the detector response to specific compounds across a range of concentrations. The library also includes other operationally relevant substances, including diamorphine (heroin), cocaine, buprenorphine, and tramadol whose drift times do not overlap with the main SCRA detection window (8.8-9.8 ms). For security reasons these details and information on the full list of substances included in the operational prison testing library are not disclosed in this study. The drug reference libraries used on the instruments in this study are identical to those used operationally in UK prisons allowing the evaluation of the effectiveness of the instruments in an operationally valid manner.

2.4.1 Determination of instrument selectivity

The selectivity of the ITMS^{TM} test systems was assessed by determining the drift times of a wide range of SCRAs across several structural classes, including the most prevalent compounds at the time the study was conducted[9], as well as emerging and prophetic compounds, AMB-4en-PICA **(16)** and MDMB-4en-PICA **(17)**, which had not yet been detected in our prison monitoring study but have the potential to enter the market and for which in-house synthesized reference standards were available. To study the variation of drift time within two closely related structural classes, the largest number of SCRAs included were valinate- or *tert*-leucinate-indole- or indazole-3-carboxamides. For all analytes, drift times were recorded for SCRAs across a wide range of analyte loading masses (0.5 to 1000 ng on sample trap). The sample traps were prepared by pipetting SCRA solutions in methanol onto clean sample traps that had been previously desorbed and run as blank samples on the ITMS^{TM} instruments. The solvent was allowed to evaporate before the sample trap was inserted into the instrument thermal desorber sampling unit. The preparation of the SCRA loaded sample traps is described in the supplementary information (Table S3.1).

Calculation of Reduced Mobility Values

Reduced mobility values (K_0) are a qualitative indicator of the identity of a gas phase ion based on the velocity of the ion in a drift/buffer gas under the influence of a homogeneous electric field. Ideally, these values should be constant for a given compound in a given drift gas, but in practice they have been found to vary, with the variations being attributed to instrumental design variations and the use of different experimental conditions, such as temperature and electric field[40]. K_0 values were calculated similarly to that described in Verkouteren, et al. (2020)[41]. For each compound, the average K_0 value was determined from K_0 values calculated from replicate analyses of SCRAs across a range of sample loads (0.5-1000 ng). The K_0 value was calculated with Equation 1 using the drift time of the sample (t_d), drift time of cocaine (t_d^{coc}), and the K_0 of cocaine (K_0^{coc}) where K_0^{coc} = 1.160 $cm^2\ V^{-1}\ s^{-1}$. Cocaine was used as the calibration compound and was provided pre-loaded onto calibration traps.

$$K_0 = (t_d^{coc}\ K_0^{coc}) / t_d \qquad \textit{Equation 1}$$

During calibration of the Itemiser® 3E, the system corrects the drift time of cocaine to always be 7.945 ms, recalculating all subsequent drift times relative to this value. Therefore, for the calculation of the K_0 values on these systems, t_d^{coc} was always 7.945 ms. For the Itemiser® 4DN, the drift time of cocaine varies with each calibration, so the drift time of cocaine from the external calibration performed before each set of samples was used as the t_d^{coc} in the calculation of the K_0 values for those samples. The values are provided in the supplementary data.

2.4.2 Determination of instrument sensitivity

To estimate instrument limit of detection (LOD) and determine the linearity of instrument response, sample traps were loaded with different SCRAs at a variety of loading masses (0.5 to 1000 ng) as described previously. LODs were determined for 4F-MDMB-BINACA **(2)**, MDMB-4en-PINACA **(3)**, Cumyl-4CN-BINACA **(5)**, Cumyl-PEGACLONE **(7)**, AB-CHMINACA **(8)**, AMB-FUBINACA **(9)**, 5F-PB-22 **(10)**, MDMB-CHMICA **(11)**, and AMB-4en-PICA **(12)** to represent a range of SCRA structural classes. Each SCRA at each loading mass was analyzed in triplicate on all five instruments (two 4DN systems used during this analysis). A quadratic regression curve of the average peak heights for each tested concentration was determined for each instrument and the LOD was estimated from either the curve (calculated LOD, cLOD) or from the instrument response to traps containing known

masses of analyte (observed LOD, oLOD). The firmware on the instruments does not enable the signal to noise ratio to be obtained from the plasmagram. The number of points used to construct the curve varied depending on the concentration above which the detector response plateaued.

2.4.3. Determination of instrument suitability using seized paper samples

For the analysis of seized paper samples previously analyzed by GC-MS, the blank sample trap was first inserted into the instrument to ensure that it was contamination free and to act as a negative control for the sample to be tested. The clean sample trap was rubbed along the surface of the sample with two fingers applying pressure from the back. Papers and card for testing ranged from a few cm^2 up to A4 size (21.0 x 29.7cm) and so trap loading is likely to have varied considerably. The sample trap was inserted into the thermal desorption sampling port of the instrument for analysis. Samples taken from each seized paper sample were run on one of each type of instrument (Itemiser® 3E or Itemiser® 4DN). Multiple instruments of the same type (three Itemiser® 3E and two Itemiser® 4DN) were used to determine the field accuracy rate for each model rather than one specific instrument. This reflects the practice of the manufacturer to use multiple instruments when setting up system libraries and substance alarms, capturing any system variability between instruments of the same design. The approach to analyse seized samples also reflects the use of different instruments across multiple prison sites testing papers infused with the same SCRAs, and thus ensuring relevance to field testing practice. If the ITMS™ result differed from the GC-MS result on a particular system, the sample was run on a second instrument of that type (e.g. Itemiser® 3E or Itemiser® 4DN) to verify the result and ensure the discrepancy was not due to a sampling or instrument error . The instrument used, drift time, peak height, and alarm identification were recorded for each sample analysis and are provided in the supplementary information (Table S6.1 and S6.2).

3. Results and Discussion

3.1 Instrument Selectivity

Ideally, from an intelligence and evidential viewpoint, a benchtop IMS screening instrument for the analysis of suspected SCRA-infused items would be able to distinguish individual SCRA compounds; differentiate SCRAs from other sample components and other drugs likely to be present in samples to avoid false positives; and be sensitive enough and have an up-to-date library to avoid false negatives. From an operational viewpoint, however, the avoidance

of false positives and negatives is more important than unambiguous compound identification. It is advantageous if all SCRA compounds provide similar results (e.g. drift times, K_0, and sensitivity) and are easily distinguished from other non-SCRA substances with little overlap in drift times.

Average drift times and K_0 values for the 21 tested SCRAs are summarized in Tables 1-3 and Figures 2 and 3, and ranged from 5.294-9.742 ms on the Itemiser® 3E systems (n=3) corresponding to K_0 values of 1.7409–0.9458 $cm^2\ V^{-1}\ s^{-1}$ and 5.218-9.699 ms, corresponding to K_0 values of 1.7664-0.9488 $cm^2\ V^{-1}\ s^{-1}$ on the Itemiser® 4DN system (n=1). Data for individual instruments are provided in the supplementary information (Tables S4.1 to S4.4). No significant effect of analyte loading mass on drift times, and therefore K_0, was observed.

We have not disclosed the specific "spice" alarms generated by each of the SCRA reference standards analyzed in this study; the compounds used to produce the library entries; or which SCRAs do not generate an alarm in the current libraries. Disclosure of such information is deemed a security risk.

The Itemiser® 3E systems in use in Scottish prisons were able to detect all of the tested reference compounds (e.g. produce a measurable peak on the plasmagram), irrespective of whether they generated an alarm or not. 15 of the 21 SCRA reference standards tested generated an alarm against the current factory set alarms whilst six did not. For the Itemiser® 3E, of the 21 SCRAs tested, 14 compounds generated system "spice" alarms and 5F-Cumyl-PEGACLONE **(7)** alarmed for "tramadol." The "tramadol" alarm simply indicates that 5F-Cumyl-PEGACLONE **(7)** has a similar drift time to the opioid tramadol on the system, a reminder that these instruments are essentially advanced presumptive test systems. The libraries present are prepared by the manufacturer in the context in which the instruments are used, i.e. they only contain substances commonly detected in prisons. The libraries can be adapted as required at the local and global level as drug markets and individual substance prevalence changes. Five of the six SCRAs which did not generate an alarm had drift times within the typical SCRA detection window (8.8-9.8 ms). In an operational context, if these five substances were to appear in case samples, trained staff would identify them as being indicative of the presence of an unknown SCRA. Samples would be submitted for further laboratory testing to confirm or refute the presence of a new SCRA or other substance of interest and substance detection libraries updated as required.

For the Itemiser® 4DN instruments, 18 of the 21 tested SCRA reference standards produced a system alarm. Fourteen of these were the same as those generated on the Itemiser® 3E systems whilst four compounds generated different alarms. The two systems use significantly different substance detection algorithms. The Itemiser® 3E algorithm is relatively simple and often uses a single drift time window (normally in the positive ionization mode for SCRAs) in combination with a peak area threshold. If the drift time of a substance analyzed on the Itemiser® 3E falls within a specific substance library detection window with a peak area above the alarm threshold, it will produce a substance alarm. The Itemiser® 4DN algorithm is more complex and its proprietary nature does not permit further investigation in this study. The remaining three SCRAs tested did not generate "spice" alarms on the 4DN with its current settings. Two of these, Cumyl-4CN-BINACA **(5)** and 5F-Cumyl-PEGACLONE **(7)**, did not generate identifiable peaks on the plasmagram. Cumyl-4CN-BINACA **(5)** has only been detected once in Scottish prisons to date, as a minor component with three other SCRAs in an infused paper; and 5F-Cumyl-PEGACLONE **(7)** has never been detected[9]. These SCRAs have been more prevalent in other jurisdictions, in particular in Germany[42]. It is important to note that these compounds do generate identifiable peaks on the plasmagram of the Itemiser® 3E systems and would be detected in submitted samples if present.

Overall, drift times were clearly influenced by structural class. All sixteen valinate- and *tert*-leucinate-indole- or indazole-3-carboxamide class SCRAs tested produced drift times between 8.8 and 9.8 ms, the two SCRAs containing a cumyl moiety produced drift times between 7.0 and 7.5 ms on the Itemiser® 3E, and the three SCRAs belonging to the quinolinyl indole-3-carboxylates class (PB-type compounds) produced drift times between 5.2 and 5.4 ms. For the Itemiser® 3E systems (Table 1 and Figure 2), 5F-Cumyl-PEGACLONE **(7)** had the least drift time variability (0.030 ms range) and Cumyl-4CN-BINACA **(5)** the most (0.247 ms range). In the instrument substance library, which determines the results required to give a system alarm, most compounds have a detection window range of 0.080 ms. As can be seen in Table 3 and Figure 3, there was some variability in drift time on the Itemiser® 4DN systems for all the compounds, with AMB-FUBINACA **(15)** (long) showing the least variability (0.069 ms) and AB-CHMINACA **(8)** showing the most variability (0.232 ms) in Region 0 and 5F-PB-22 **(20)** showing the least variability (0.038 ms) and AMB-4en-PICA **(16)** showing the most variability (0.385 ms) in Region 1. Not all of the compounds are included in Figure 3 because there were only three data points available, however all data is provided in Table 2.

The average K_0 values for all SCRAs tested in this study are shown in Table 3 and are compared to available literature values. Data for individual instruments is provided in the supplementary information (Table S4.1 and S4.2). Due to the general user interface (GUI) / software available on the Itemiser® instruments, the resolution between compounds cannot be directly calculated; instead the resolution between compounds can be more generally discussed using the differences between K_0 values of two compounds. According to the UNODC "Recommended Methods for the Identification and Analysis of Synthetic Cannabinoid Receptor Agonists in Seized Materials" [34], IMS cannot reliably discriminate between compounds with differences in K_0 values of less than 0.025 $cm^2 V^{-1} s^{-1}$. Metternich et al (2019) determined that to obtain a resolution of 0.75 between analyte peaks, there needs to be a > 0.15 ms and > 0.013 $cm^2 V^{-1} s^{-1}$ difference in drift time and reduced mobility value respectively, between the analyte peaks[35]. For full baseline resolution (Rs = 1.5) the difference had to be > 0.35 ms and > 0.024 $cm^2 V^{-1} s^{-1}$. In our study, the mean K_0 values of 4F-MDMB-BINACA **(2)** and MDMB-4en-PINACA **(3)** differ by 0.0070 $cm^2 V^{-1} s^{-1}$ and so cannot be reliably distinguished and both alarmed as "spice 9." The 95% confidence intervals of AB-CHMINACA **(14)** and MDMB-4en-PINACA **(3)** overlapped on both the 3E and Region 1 of the 4DN. This is not deemed problematic in seized samples as AB-CHMINACA **(14)** has not been detected in any seized papers from Scottish prisons since the start of sample collection (June 2018) and was controlled by The People's Republic of China in 2015 and so is likely to have disappeared soon after from the illicit market[43,44]. In addition, the alarm for AB-CHMINACA **(14)** is typically turned off for in-field operations and in the event that AB-CHMINACA **(14)** reappears, it would be picked up with a "spice 9" alarm.

The value of 0.0250 $cm^2 V^{-1} s^{-1}$ is also important to consider when analyzing the range of K_0 values calculated for one compound. Ideally, the K_0 values for one compound should not have a range greater than 0.0250 $cm^2 V^{-1} s^{-1}$ (mean $K_0 \pm 0.0125$ $cm^2 V^{-1} s^{-1}$) or it could potentially be discriminated as two separate compounds by the instrument. This is important because if the instrument can discriminate between two samples of the same compound, it could lead to misidentifications or false negatives. On the Itemiser® 4DN system, the range of K_0 values was less than 0.0250 $cm^2 V^{-1} s^{-1}$ for all compounds, except 5F-PB-22 in Region 0, AMB-4en-PICA **(16)** in Region 1, and AB-CHMINACA **(14)** in both regions. These three compounds had high drift variability (see supplementary information for additional instrument-specific data), with drift time standard deviations 4-20 times greater than for the other compounds. Potential

explanations for the wide drift time range include the possibility of a partial breakdown of the substances during the sample desorption and ionization process and the formation of multiple adducts with different but unresolved drift times. As the sample desorption settings and ionization chamber settings are not user adjustable it was not possible to explore this further in this study. 5F-PB-22 and AB-CHMINACA are historical SCRAs that have not been detected in Scottish prisons since the start of the current monitoring program in June 2018, AMB-4en-PICA has not yet been detected, and Itemiser® 4DN systems are not yet in use in Scottish prisons.

On the Itemiser® 3Es, the range of K_0 values were less than 0.0250 $cm^2\ V^{-1}\ s^{-1}$ for all compounds, except for Cumyl-4CN-BINACA **(5)**, with a range of 0.0446 $cm^2\ V^{-1}\ s^{-1}$ across all instruments. This large range is likely due to a difference in the performance of Instrument 1 compared to Instrument 2 and 3 (see supplementary data). The K_0 value of Cumyl-4CN-BINACA **(5)** on Instrument 1 is different enough from that of the other instruments that it would be distinguishable as a separate compound and since all instruments share the same substance library, this much variability between instruments could lead to misidentifications or false negatives. The reason for the difference in K_0 values for one compound out of the 21 SCRAs tested on one of the three Itemiser® 3E systems tested is unknown. When library entries are created by the instrument manufacturer, multiple instruments are used to generate the substance drift time and drift time detection window. In an ideal situation, given the results obtained, Cumyl-4CN-BINACA **(5)**, could be tested on a larger number of instruments to determine whether or not the K_0 value obtained on Instrument 1 was an outlier or if the data is indicative of greater inherent drift time variability for this substance. In the latter situation, the substance drift time detection window would be widened to ensure that any samples containing this SCRA would fall within the detection window and generate a system alarm.

Yanini, et al. (2018) reported a K_0 value for Cumyl-4CN-BINACA **(5)** of 1.022[38], 0.2682 $cm^2\ V^{-1}\ s^{-1}$ lower than the K_0 value found on the Itemiser® 3E in this study, and a K_0 value for AMB-CHMICA **(6)** of 0.968, 0.0387 $cm^2\ V^{-1}\ s^{-1}$ lower than that found on the Itemiser® 3E in this study. In this study, 5F-PB-22 **(20)** and PB-22 **(9)** had much higher K_0 values (1.7400 and 1.7409 respectively) than previously reported (0.9995 and 0.9917 respectively)[35] on instruments of a different design. K_0 values for valinate- and leucinate-indazole- and indole-3-carboxamides, AB-CHMINACA **(14)**, AB-FUBINACA **(19)**, AMB-FUBINACA **(15)**, MDMB-CHMICA **(21)**, 5F-AMB-PINACA **(12)**, and 5F-MDMB-PINACA **(4)** were within

0.0250 cm^2 V^{-1} s^{-1} of previously reported values. This indicates that the relatively large differences observed for the K_0 values generated by different manufacturer's IMS systems (Smiths Detection IONSCAN and Rapiscan Systems Itemiser® 3E) for Cumyl-4CN-BINACA **(5)**, PB-22 **(9)**, and 5F-PB-22 **(20)** are related to instrument design features (e.g. electric field strength or system temperatures) and/or differential adduct formation in the ionization chamber, the investigation of which is outside the scope of this study. All previous published IMS studies involving SCRAs[34-38] have been carried out using IONSCAN systems. This is the first study to report SCRA data generated on Rapiscan Itemiser® systems and therefore the first time this difference in K_0 has been noted. Whilst the difference in K_0 values between the different systems is of scientific interest and worthy of further investigation, the finding has no operational impact. Substance libraries are generated independently by instrument manufacturers and are not shared across different instrument suppliers.

K_0 values have previously been reported for a range of NPS, including SCRAs[34–38,41], and can often be correlated with molecular mass. A strong inverse relationship between K_0 and analyte molecular mass has previously been demonstrated for fentanyl and fentanyl analogues[41], phenethylamines[34], and SCRAs[38]. All available K_0 data for SCRAs from previous studies[34–38] have been combined with the averaged K_0 data from the Itemiser® 3E instruments used in this study and plotted against molecular mass (Figure 4a). Although there is an apparent inverse relationship between reduced mobility and molecular mass for many SCRAs, the relationship may be class specific. If data for cumyl-type compounds and quinolinyl (PB-type compounds) are removed, the inverse relationship becomes clearer for the remaining compounds from all studies (Figure 4b; K_0 = -0.0014 (Molecular Mass) + 1.5136; R^2 = 0.6974) and this study (Figure 4c; K_0 = -0.0013 (Molecular Mass) + 1.4790; R^2 = 0.5447).

Although the currently most prevalent valinate- and *tert*-leucinate-indole- and indazole-3-carboxamide SCRAs have drift times between 8.8-9.8 ms referred to operationally as the "typical SCRA drift time window," SCRAs belonging to markedly different compound classes e.g. γ-carboline (e.g. Cumyl/5F-Cumyl PEGACLONE) and quinolinyl compounds (e.g. PB-type SCRAs) may have drift times outside of this window. This clearly demonstrates the need to couple operational IMS scanning of mail and other items for SCRAs with a more detailed seized sample 'dip' sampling and rapid laboratory analysis program, rapid information sharing, up-to-date training, and close engagement with national and international early warning

systems. This ensures up-to-date local intelligence on circulating drugs is maintained and IMS scanning systems remain effective.

3.2 Instrument Sensitivity

Although IMS systems are used for presumptive screening rather than in an evidential context, and there is no suggestion that IMS systems should be used for quantitative analysis, it is useful to determine their detection limitations. IMS systems are often used to detect trace and ultra-trace levels of drugs in security settings such as airports and therefore need to be highly sensitive; however, SCRAs, although highly potent psychoactive substances, are often present at much higher concentrations in infused papers seized in prisons. Previous work by our group has shown that SCRA concentrations in infused papers in Scottish prisons range from <0.05 to 1.17 mg/cm^2 paper[9]. SCRAs representing a range of market-relevant structural classes were selected to study instrument quantitative response and estimate the limit of detection (LOD) for each SCRA compound as expressed by mass of analyte on the sample trap. It is important to note that the mass of analyte on the sample trap cannot be directly compared to the concentration of SCRAs in infused papers because it is not known how much of the analyte is collected by the sample trap during sampling. Additionally, any matrix effects due to other substances present on the papers (inks, waxes etc) being transferred to the sample trap cannot be quantified as the papers sampled are highly variable and the relative recovery efficiencies of the materials present is unknown.

The average detector response for the selected SCRA compounds across the tested analyte mass range for all three Itemiser® 3E instruments is provided in Figure 5. The replicate data (n=3) for each of the SCRA masses from all three Itemiser® 3E instruments (n=9 in total) is provided in the supplementary information (Table S5.1 and S5.2 and Figure S5.1-3). For all SCRAs there is a non-linear (quadratic) increase in instrument response over a limited analyte mass range until the detector response plateaus. The reason for this plateauing may be two-fold: saturation of the ionization process (there is only so much ionization that can occur in the ionization chamber) or saturation of the detector. Metternich, et al. (2019) reported a linear increase for the IONSCAN600 IMS instrument over a very limited loading mass range (0.7-3.6 ng SCRA)[35] but did not report response plateauing although this is likely to have occurred. Armenta, et al. (2014) and Gwak, et al. (2015) also reported a linear increase for the IONSCAN-LS and IONSCAN 400B across very limited loading mass ranges of 0.1-1 ng SCRA and 0.05-3 ng SCRA, respectively without any report of response plateauing[36,37]. For

the 3E and 4DN, an approximate quadratic increase in detector response for all compounds was observed prior to detector response plateauing. Although only a small number of data points were available for most SCRAs in this quadratic response region, quadratic curves were fitted and the curves, R^2 values, and estimates of the instrument LOD (observed LOD, oLODs) and the LOD calculated from the quadratic line of best fit (calculated LOD, cLODs) are provided in the supplementary information. oLODs are displayed as a range of concentrations from the last sample loading mass to be detected to the first loading mass that was not detected (peak height of 0). For the Itemiser® 3E instruments, the cLODs ranged from 0.5 to 12.9 ng, whereas the oLODs ranged from 0.5 to 100 ng. AB-CHMINACA (**14**) had the highest LODs, calculated by either method. LODs were found to vary to a relatively small extent between the instruments used in this study.

For the Itemiser® 4DN instruments, cLODs ranged from 8.5 to 100.0 ng and 21.1 to 100.0 ng, for Region 0 and 1 data respectively, and the oLODs ranged from 5 to 500 ng and 20 to 1000 ng, respectively. Overall the data indicates that Region 0 has better sensitivity than Region 1, while Region 1 was found to have better selectivity. Since the region used in the detection of a compound can be dictated in the substance library, the preference for improved selectivity or sensitivity is likely to be customized for each compound on this instrument. It is difficult to compare the responses of the two models as the Itemiser® 4DN instrument uses a more advanced proprietary algorithm for compound detection and identification than the Itemiser® 3E. However, the 3E had lower LOD values than the 4DN for all compounds although the difference is unlikely to be of operational significance, considering the SCRA concentrations present in infused papers circulating in prisons. Previous studies using Smiths Detection IONSCAN-LS, IONSCAN 400B, and IONSCAN600 have reported lower limits of detection for NPS but have used different calculation methods and calibration ranges. Armenta et al. (2015) report LODs ranging from 0.02-0.05 ng using a five point calibration over a 0.1-1 ng linear calibration range[36]; Gwak and Almirall (2015) reported LODs ranging from 0.04-0.08 ng over a calibration range of 0.1-0.5 ng or 0.3-0.34 ng over a calibration range of 50-1500 ng[37]; and Metternich et al. (2019) reported LODs of 0.7-3.6 ng using a calibration range of 1-8 ng[35].

3.3 Qualitative analysis of SCRAs in seized papers from Scottish prisons by GC-MS

To test the applicability and reliability of the benchtop ITMS™ systems for the detection of SCRAs in infused papers in a controlled manner and confirm the detection of the most prevalent SCRAs in circulation in Scottish prisons up to December 2019, samples were first sub-sampled and analyzed by GC-MS (and the identifications of any SCRAs present confirmed by UPLC-QTOF-MS). A total of 392 paper samples seized from four Scottish prisons were qualitatively analyzed by GC-MS. Controlled substances were detected on 189 samples; 182 (46%) samples were positive for one or more SCRAs, and controlled drugs other than SCRAs were detected in 7 samples. Of those testing positive for SCRAs, 46 contained 4F-MDMB-BINACA **(2)**; 44 contained 5F-MDMB-PICA **(1)**; 38 contained 5F-MDMB-PINACA (5F-ADB) **(4)**; 14 contained MDMB-4en-PINACA **(3)**; 3 contained AMB-FUBINACA **(9)**; and 1 contained AMB-CHMICA **(6)**, on their own. Mixtures of SCRAs were detected on 36 paper samples; 18 with MDMB-4en-PINACA **(3)** and 4F-MDMB-BINACA **(2)**; 9 with MDMB-4en-PINACA **(3)**, 4F-MDMB-BINACA **(2)**, and 5F-MDMB-PICA **(1)**; 5 with 4F-MDMB-BINACA **(2)** and 5F-MDMB-PICA **(1)**; and 4 with 5F-MDMB-PINACA **(4)** and 5F-MDMB-PICA **(1).** The qualitative data for prisons 1-3 seized between June 2018-September 2019 (n=276) as reported in Norman et al. (2020) are compared with the additional data relating to samples seized from prison 1 between September 2019 and 18 December 2019 (n=58) and samples from prison 4 (n=59) in Figure 6. The data demonstrates the increasing prevalence of MDMB-4en-PINACA **(2)** and 4F-MDMB-BINACA **(3)** and the decreasing prevalence of other SCRAs in the prisons included in the project over the study period.

3.4 Qualitative analysis of SCRAs in seized papers from Scottish prisons by ITMS™

Yanini, et al (2019) describe the use of IMS for the detection of eight SCRAs, including 5F-MDMB-PINACA (5F-ADB) **(4)**, Cumyl-4CN-BINACA **(5)**, and AMB-CHMICA (MMB-CHMICA) **(6)** in apparently high purity seized sample powders[38]. Metternich, et al. (2019) reported the detection of 25 SCRAs (9 of which are also included in this study), in different matrices, including herbal mixtures, papers, cosmetic products, and liquid food samples. The method was applied to 36 casework samples, 12 of which were positive for SCRAs and only one was a SCRA-infused paper[35]. In this study, 392 seized papers suspected to be infused with SCRAs were analyzed, the largest study reported to date using IMS/ITMS™ for the detection of SCRAs.

Seized paper samples that had been previously analyzed by GC-MS (using approximately 2 x 1cm^2 sub-samples cut from the paper) were analyzed on the Itemiser® 3E and 4DN ITMS™ systems. An overview of the ITMS™ results in comparison to the GC-MS data is provided in Tables 4 and 5. As some samples gave rise to multiple alarms, the total number of alarms in Table 5 is not equivalent to the number of samples. In addition, in the event that the ITMS™ result differed from the GC-MS result, the sample was run a second time on a different instrument of the same type in order to corroborate the findings. The results were the same in both runs in all cases, except two samples for the Itemiser® 3E (FL19/0104 and FL19/0206-A) and one sample for the Itemiser® 4DN (FL19/0022-4). For these samples, the data from both runs are included in the analysis, so the total sample count for the Itemiser® 3E appears to be 394 and the total sample count for the Itemiser® 4DN appears to be 393. The complete ITMS™ analytical data for all the samples is provided in the supplementary information (Table S6.1 and S6.2).

The level of agreement between the ITMS™ and GC-MS results was similar between the two Rapiscan Itemiser® systems tested: 91.1% for the Itemiser® 3E and 92.9% for the Itemiser® 4DN systems, demonstrating the suitability of their use for the presumptive detection of SCRAs in infused papers in prisons. Papers which gave a negative result for SCRAs by GC-MS but a positive result on ITMS™ were investigated further (Table 4). Often there are several paper samples, from different sources and of different visual appearance in a single seizure and these are placed in the same evidence bag for testing. Where some of the papers in the evidence bag are infused with SCRAs and others are not, cross contamination is likely to occur. In such cases, 2 x 1cm^2 sub-samples taken for GC-MS analysis could give a negative SCRA result, but the same papers, sampled over a larger surface area with the sample trap could pick up enough of the SCRA to be detected on the ITMS™ systems. Taking the factor of cross contamination of samples stored together in evidence bags into account, the level of agreement for SCRA detection between the ITMS™ and GC-MS increases to 94.2% and 95.7% for the Itemiser® 3E and Itemiser® 4DN, respectively.

The majority of the false negative results observed on both ITMS™ instruments were related to samples where only trace amounts of SCRA were indicated by the GC-MS. This in turn indicated that the sample likely did not have purposeful addition of the SCRA but that the substances were present as a result of coming into contact with SCRA infused papers. When

the samples were tested using ITMS™, no SCRAs could be detected. Other false negative results had observable peaks on the plasmagram just outside the drift time region for one of the "spice" alarms, but would likely have been set aside by trained staff for further analysis. For example, sample FL20/215-E had a large peak near the drift range of a "spice 9" alarm on both the 3E and 4DN instruments, but it did not alarm (for more information see section 6 of the supplementary information). Many of the potential false positives on the Itemiser® systems related to alarms for cocaine and buprenorphine. A larger surface area of the paper is sampled during ITMS™ analysis than GC-MS and the presence of these compounds is more likely to be due to particulate material adhering to the paper surface than materials infused into the paper. This means they will be detected on the ITMS™ systems and not the GC-MS method. Additionally, buprenorphine has a retention time greater than the GC run time (12 minutes) and is not detected in the SCRA screening method.

On the Itemiser® 3E instruments, 185 samples alarmed for one or more SCRAs with a total of 192 "spice" alarms across all samples tested. The frequency of the recorded peak heights for all sample analyses that generated a "spice" alarm on the Itemiser® 3E can be seen in Figure 7a. Analysis of almost all of the SCRA infused papers sampled resulted in peak heights well above the manufacturer configured alarm thresholds (not shown for security reasons) in agreement with our previous work showing the relatively high concentrations of the SCRAs present[9]. Of the 192 "spice" alarms generated, only 19 had peak heights below 1000. Of these, GC-MS analyses demonstrated that 2 of these samples were found to have only trace amounts of SCRA present and 4 were most likely cross-contamination of SCRAs from being stored in the same evidence bag with a considerably more concentrated SCRA-positive sample.

On the Itemiser® 4DN systems, 187 samples alarmed for one or more SCRAs with a total of 210 "spice" alarms across the samples. The frequency of the peak heights for all "spice" alarms on the 4DN can be seen in Figure 7b. Almost all of the samples had detector response peak heights well above the alarm thresholds with almost 60% of the samples having peak heights over 6000 in both Region 0 and Region 1. Of the 210 alarms, there were 29 and 22 samples that were below a peak height of 2000 in Region 0 and Region 1, respectively. The "spice 6" alarm on the 4DN systems often alarmed incorrectly and over a wide range of drift times meaning that there could be an increased chance of false positive detections for this substance. The compound used to generate this alarm was first detected in Europe in 2014 and its

production and export was controlled by the People's Republic of China in 2015[43,44] and this compound is now rarely, if ever, detected on the illicit market.

Despite having higher LODs, as estimated in this study, compared to those reported by other studies using different instruments and different LOD calculation methods, both ITMS™ models tested here are fit for purpose for the detection of SCRAs at the concentrations commonly observed in infused papers in Scottish prisons. The amount of analyte introduced into the instrument via the sample trap will inevitably depend on the size of the paper being sampled and the method of sampling. The data suggests that the systems are so sensitive, that as well as detecting SCRAs in infused papers at relevant concentrations, they may pick up trace levels of SCRAs in non-infused samples which have been in contact with or stored with infused papers, indicating that in the context of the screening of SCRA infused papers in prisons, increased sensitivity is not required. The training of staff in effective sampling and cross-contamination avoidance is therefore of paramount importance.

The drift time variability of all the "spice" alarms on the Itemiser® 3E is depicted in Figure 8a. In the substance library, the "spice 4" alarm is set to have a possible detection window of 0.060 ms, but in this dataset it had a range of 0.076 ms. The "spice 5" alarm is set to have a possible range of 0.060 ms and had an observed range of 0.061 ms in this dataset. The "spice 9" alarm had the second highest variability with a range of 0.106 ms, when the substance library is only set to have a possible range of 0.080 ms. This is unsurprising as this alarm is detecting both 4F-MDMB-BINACA (**2**) and MDMB-4en-PINACA (**3**) leading to broader, unresolved peaks on the instrument plasmagram when SCRA mixtures are present in infused samples, as they often are. The "spice 8" alarm had the greatest drift time variability with a range of 0.206 ms, which reflects the wider detection window (0.115 ms) for this compound in the substance library. This may in part be due to the number of infused paper samples tested that have mixtures of 5F-MDMB-PICA (**1**) and 5F-MDMB-PINACA (**4**) as these compounds have similar drift time detection windows. The Itemiser® 4DN seems to have greater drift time variability (Figure 8b) and seems to be more greatly affected by mixtures of SCRAs than the 3E. This greater variability in drift time on the Itemiser® 4DN is likely at least part of the reason for the greater number of incorrect alarm identifications.

Overall, this data indicates that, despite having set detection windows in the substance library, both the Itemiser® 3E and 4DN can correctly identify SCRA compounds that lie just outside

the detection windows of known compounds. This is due to the ITMS^{TM} systems alarming when essentially any amount of a sample peak on the plasmagram falls into a previously set alarm threshold, not just when the apex of the peak does. This is beneficial for detecting SCRAs with similar, but slightly different drift times within known "typical" drift time ranges, e.g. the detection of AMB-CHMICA **(6)** and MDMB-4en-PINACA (**3**) on the Itemiser® 3E system on alarms developed for other compounds.

This is further demonstrated by the provisional identification of three SCRAs detected in Scottish prisons for the first time. In the absence of reference standards for these substances in our laboratory at the time of this study, their identification is based on analytical data (GC-MS and UPLC-PDA-QToF-MS spectra) and examples of the high resolution mass spectral data are provided in section 7 of the supplementary information), as well as comparison with spectral libraries and publicly available spectra[45–50]. 5F-EMB-PICA (**22,** EMB-2201**,** ethyl 2-[[1-(5-fluoropentyl)indole-3-carbonyl]amino]-3-methyl-butanoate) and 4F-MDMB-BICA (**23**, methyl 2-[[1-(4-fluorobutyl)indole-3-carbonyl]amino]-3,3- dimethyl-butanoate) were first reported to the European early warning system (EU-EWS) in July 2020, based on seizures on the 3rd and 31st March 2020 respectively[51,52], and the Response 2 Project by the Hungarian Institute for Forensic Sciences, based on seizures on the 20th and 15th of July 2020 respectively[53]. These SCRAs were first identified on infused papers seized in three different Scottish prisons (prisons 1-3) between May and August 2020. 4F-MDMB-BICA was detected as the only SCRA present in 4 samples and 5F-EMB-PICA was detected as the only SCRA present in one sample and with MDMB-4en-PINACA in three samples (see Table S1). 5F-MPP-PICA (**24**, MPhP-2201, methyl 2-[[1-(5-fluoropentyl)indole-3-carbonyl]amino]-3-phenylpropanoate) was first reported to the EU-EWS and by the Response 2 Project in 2018[53,54] and was identified Scotland for the first time in prison 2 in a sample seized in July 2020.

Although these SCRAs are not included in the ITMS^{TM} instrument libraries, they had drift times and reduced mobility values close enough to SCRAs in the instrument substance library to produce a system "spice" alarm (5F-EMB-PICA **(22)**, drift time = 9.435 ms, K_0 = 0.9768 $cm^2\ V^{-1}\ s^{-1}$ (n=1); 4F-MDMB-BICA **(23)**, drift time = 9.135 +/- 0.014 ms, K_0 = 1.0088 +/- 0.0016 $cm^2\ V^{-1}\ s^{-1}$ (n=4) ; and 5F-MPP-PICA **(24)**, drift time = 9.671 ms, K_0 = 0.9530 $cm^2\ V^{-1}\ s^{-1}$ (n=1)). Where 5F-EMB-PICA was present as a minor component with MDMB-4en-PINACA (estimated from GC-MS peak area), the alarm generated was that expected for MDMB-4en-PINACA (and 4F-MDMB-BINACA).

5F-EMB-PICA had a similar drift time and K_0 value to 5F-MDMB-PICA; the only structural difference between the two compounds (Figure 1) is the presence of an ethyl ester on the "linked group" of the former and a methyl ester in the latter. 4F-MDMB-BICA had a similar drift time to 4F-MDMB-BINACA as the only structural difference is that the former has an indole "core" group and the latter an indazole "core" group. It is suggested that these minor structural changes have little effect on the ion mobility properties and therefore drift times. The drift time for 5F-MPP-PICA, which has a benzyl moiety in the "head" group, is similar to the library entry for 5F-AKB48 (5F-APINACA, data not shown), the latter SCRA having an adamantyl moiety on the "head" group.

4. Conclusion

The Rapiscan Itemiser® 3E and Itemiser® 4DN systems were evaluated for their reliability to rapidly detect SCRA infused papers in prisons in an operationally relevant context. Our analysis has confirmed that both instrument types were effective with an agreement of up to 95% with laboratory-based GC-MS analysis. The Itemiser® 3E was found to be better for use in the detection of SCRAs due to its ability to detect cumyl compounds (Cumyl-4CN-BINACA and 5F-Cumyl-PEGACLONE), unlike the Itemiser® 4DN with its current detection settings. There were some inconsistencies in the K_0 values between this study and those reported in previously published studies, which is likely due to differences in the electric field strength or temperature between different manufacturers' instruments. In particular, compounds not in the most prevalent valinate- and *tert*-leucinate-indazole and indole SCRA classes (e.g. 5F-PB-22, Cumyl-4CN-BINACA, and 5F-Cumyl-PEGACLONE) had considerably lower drift times compared to what is operationally often referred to as the SCRA drift time window of 8.8-9.8 ms.

As observed in this study, any new SCRAs emerging on the market may generate drug detection alarms due to their structural similarity to the compounds already in the library. However, the importance of training operational, non-scientific staff in prisons to identify significant peaks that do not generate alarms, rather than simply responding to pre-set alarms, has been highlighted. To keep SCRA detection libraries on IMS/ITMS™ systems up to date it is recommended that (i) in situ screening of mail for SCRAs by front-line prison staff using IMS/ITMS™ should operate in tandem with effective laboratory-based prison drug monitoring programs to rapidly identify and communicate emerging drug threats; (ii) test samples suspected of being infused with SCRAs that do not generate an alarm but produce peaks within

a typical SCRA detection range should be submitted for priority confirmatory laboratory-based testing; (iii) system substance libraries should be updated by trained scientific staff, at a local level if possible, to respond to locally emerging drug threats; and (iv) near real-time data and intelligence should be shared to maintain drug detection libraries to ensure their operational relevance and effectiveness.

Overall, this study found the Rapiscan Itemiser® ITMS™ systems tested to be effective instruments for the rapid detection of SCRA infused papers and used effectively, will help reduce the supply of SCRAs in the prisons and identify emerging threats. Of course, taking a pragmatic view, it is recognized that stopping or reducing one particular supply route by introducing routine and effective scanning of mail may cause alternative smuggling methods to be developed to supply a well-established prison market. These potential changes in supply methods may in turn cause an increase in risk (the law of unintended consequences) and this possibility also needs to be considered.

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Conflicts of Interest

The five ITMS™ instruments and all sample traps (sampling devices) used in this study were provided by Rapiscan Systems Limited. Although technical and operational matters were discussed, Rapiscan Systems Limited staff were not involved in the preparation of this manuscript.

Supplementary Information

Supplementary data to this article can be found online at:

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Table 1. Synthetic Cannabinoid Receptor Agonist (SCRA) drift times on three Itemiser® 3E instruments.

SCRA class	SCRA	Atomic mass (g/mol)	Instrument #1			Instrument #2			Instrument #3			Overall		
			Mean	Range	n	Mean	Range	n	Mean	Range	n	mean	s.d.	n
Quinolinyl indole-3-carboxylates	PB-22	358.4	5.294	0.001	4	5.281	0.006	4	5.307	0.007	4	5.294	0.011	12
	5F-PB-22	376.4	5.384	0.021	21	5.285	0.035	25	5.295	0.017	22	5.294	0.010	68
	FUB-PB-22	396.4	5.295	0.011	4	5.286	0.017	4	5.305	0.007	4	5.295	0.009	12
Cumyl indazole-3-carboxamide	Cumyl-4CN-BINACA	360.5	7.037	0.034	17	7.205	0.095	21	7.205	0.081	16	7.152	0.081	54
γ-carbolinone	5F-Cumyl-PEGACLONE	372.5	7.476	0.015	16	7.477	0.022	20	7.485	0.024	18	7.479	0.008	54
Valinate- and leucinate- indole and indazole-3-carboxamides	AMB-4en-PICA	342.4	8.938	0.026	22	8.951	0.057	24	8.937	0.041	23	8.943	0.012	70
	MDMB-4en-PICA	356.5	9.190	0.008	3	9.191	0.008	3	9.207	0.008	3	9.196	0.009	9
	AB-CHMINACA	356.5	9.126	0.052	13	9.146	0.082	17	9.151	0.052	16	9.142	0.020	46
	MDMB-4en-PINACA	357.5	9.142	0.022	19	9.157	0.029	23	9.146	0.021	18	9.149	0.009	60
	5F-ADB-PINACA	362.5	8.804	0.019	3	8.845	0.025	3	8.877	0.029	3	8.842	0.033	9
	4F-MDMB-BINACA	363.4	9.084	0.038	21	9.085	0.085	28	9.085	0.040	25	9.085	0.014	74
	AB-FUBINACA	368.4	8.994	0.009	3	9.032	0.018	4	9.026	0.012	3	9.019	0.018	10
	AMB-CHMICA	370.5	9.148	0.008	3	9.159	0.013	3	9.157	0.010	3	9.155	0.007	9
	5F-MDMB-PICA	376.5	9.395	0.010	3	9.387	0.026	3	9.388	0.006	3	9.39	0.008	9
	5F-MDMB-PINACA	377.5	9.293	0.004	3	9.317	0.021	3	9.312	0.012	3	9.307	0.013	9
	5F-AMB-PINACA	363.4	9.043	0.010	3	9.072	0.019	3	9.060	0.009	3	9.058	0.014	9
	ADB-FUBINACA	382.4	9.152	0.019	3	9.166	0.071	5	9.189	0.030	3	9.169	0.024	11
	AMB-FUBINACA	383.4	9.291	0.034	21	9.304	0.034	24	9.303	0.046	21	9..299	0.011	66
	ADB-CHMINACA	370.5	9.269	0.023	4	9.305	0.045	4	9.335	0.021	3	9.300	0.032	11
	MDMB-CHMICA	384.5	9.737	0.038	16	9.745	0.024	23	9.743	0.041	21	9.742	0.010	60
	MDMB-FUBINACA	397.4	9.543	0.013	3	9.556	0.026	3	9.567	0.017	3	9.555	0.014	9

Table 2. Synthetic Cannabinoid Receptor Agonist (SCRA) drift times on Itemiser® 4DN instrument.

SCRA class	SCRA	Atomic mass (g/mol)	Region 0			Region 1		
			Mean	SD	n	Mean	SD	n
Quinolinyl indole-3-carboxylates	PB-22	358.4	5.257	-	1	5.287	0.02	3
	5F-PB-22	376.4	5.218	0.071	16	5.298	0.004	6
	FUB-PB-22	396.4	5.257	0.038	3	5.287	0.015	3
Valinate- and leucinate-indole and indazole-3-carboxamides	AMB-4en-PICA	342.4	8.954	0.010	15	8.808	0.146	12
	MDMB-4en-PICA	356.5	9.171	0.03	3	9.007	0.292	3
	AB-CHMINACA	356.5	8.995	0.083	8	8.886	NA	1
	MDMB-4en-PINACA	357.5	9.170	0.019	17	9.167	0.014	14
	5F-ADB-PINACA	362.5	8.801	0.185	3	8.753	0.059	2
	4F-MDMB-BINACA	363.4	9.122	0.017	16	9.120	0.013	14
	AB-FUBINACA	368.4	9.046	0.021	3	9.061	0.007	2
	AMB-CHMICA	370.5	9.155	0.005	3	9.164	0.036	3
	5F-MDMB-PICA	376.5	9.385	0.029	3	9.427	0.020	3
	5F-MDMB-PINACA	377.5	9.241	0.072	3	9.29	0.019	3
	5F-AMB-PINACA	363.4	9.073	0.016	3	9.08	0.004	3
	ADB-FUBINACA	382.4	9.068	0.235	3	9.085	0.042	2
	AMB-FUBINACA (L)	383.4	9.289	0.016	15	9.281	0.013	13
	AMB-FUBINACA (S)	383.4	9.358	0.027	14	9.358	0.016	11
	ADB-CHMINACA	370.5	9.203	0.104	3	9.216	0.069	3
	MDMB-CHMICA	384.5	9.699	0.015	13	9.697	0.010	10
	MDMB-FUBINACA	397.4	9.582	0.009	3	9.599	0.013	3

Table 3. Average reduced mobility (K_0) values for SCRAs analyzed using Itemiser® 3E and Itemiser® 4DN instruments for all compounds. CI is the 95% confidence interval where the confidence interval is $K_0 \pm CI$.

SCRA class	SCRA	Itemiser® 3E					Itemiser® 4DN										Literature values	
							Region 0					Region 1						
		K_0	SD	Range	n	CI	K_0	SD	Range	n	CI	K_0	SD	Range	n	CI	K_0	Ref
Quinolinyl indole-3-carboxylates	PB-22	1.7409	0.0037	0.0102	12	0.0021	1.7514	-	-	1	-	1.7403	0.0037	0.0066	3	0.0042	0.9917	[35]
	5F-PB-22	1.7408	0.0032	0.0175	68	0.0008	1.7664	0.0195	0.0682	30	0.0070	1.7387	0.0032	0.0099	10	0.0020	0.9995	[35]
	FUB-PB-22	1.7406	0.0031	0.0105	12	0.0017	1.7513	0.0071	0.0126	3	0.0080	1.7404	0.0028	0.0049	3	0.0031		
Cumyl indazole-3-carboxamide	Cumyl-4CN-BINACA	1.2888	0.0147	0.0446	54	0.0039	-	-	-	-	-	-	-	-	-	-	1.022	[38]
γ-carbolinone	5F-Cumyl-PEGACLONE	1.2322	0.0013	0.0049	54	0.0003	-	-	-	-	-	-	-	-	-	-		
Valinate- and leucinate-indole and indazole-3-carboxamides	AMB-4en-PICA	1.0306	0.0013	0.0084	70	0.0003	1.0319	0.0038	0.0114	29	0.0014	1.0473	0.0173	0.0434	23	0.0071		
	MDMB-4en-PICA	1.0022	0.0010	0.0027	9	0.0006	1.0039	0.0016	0.0033	3	0.0019	1.0217	0.0178	0.0329	3	0.0202		
	AB-CHMINACA	1.0081	0.0022	0.0091	46	0.0006	1.0168	0.0112	0.0262	16	0.0055	1.0120	0.0135	0.0312	5	0.0118	0.9975	[35]
	MDMB-4en-PINACA	1.0073	0.0010	0.0042	60	0.0003	1.0043	0.0021	0.0074	35	0.0007	1.0035	0.0012	0.0052	29	0.0004		
	5F-ADB-PINACA	1.0423	0.0039	0.0112	9	0.0026	1.0462	0.0126	0.0218	3	0.0142	1.0513	0.0050	0.0071	2	0.0069		
	4F-MDMB-BINACA	1.0145	0.0016	0.0096	74	0.0004	1.0068	0.0014	0.0062	31	0.0005	1.0089	0.0017	0.0061	28	0.0006		
	AB-FUBINACA	1.0217	0.0021	0.0069	12	0.0012	1.0178	0.0012	0.0024	3	0.0014	1.0155	0.0006	0.0008	2	0.0008	1.0123	[35]
	AMB-CHMICA	1.0067	0.0008	0.0023	9	0.0005	1.0056	0.0003	0.0005	3	0.0003	1.0040	0.0022	0.0039	3	0.0025	0.9680	[38]
	5F-MDMB-PICA	0.9815	0.0009	0.0027	9	0.0006	0.9810	0.0017	0.0030	3	0.0019	0.9761	0.0011	0.0021	3	0.0012		
	5F-MDMB-PINACA	0.9902	0.0014	0.0040	9	0.0009	0.9964	0.0042	0.0078	3	0.0048	0.9904	0.0010	0.0020	3	0.0012	0.9917 0.9840	[35] [38]
	5F-AMB-PINACA	1.0174	0.0016	0.0046	9	0.0010	1.0148	0.0009	0.0018	3	0.0010	1.0133	0.0002	0.0004	3	0.0003	1.0123	[35]
	ADB-FUBINACA	1.0045	0.0022	0.0066	9	0.0014	1.0154	0.0138	0.0264	3	0.0157	1.0128	0.0033	0.0047	2	0.0046		
	AMB-FUBINACA (long)	0.9910	0.0011	0.0066	66	0.0003	0.9905	0.0026	0.0097	31	0.0009	0.9887	0.0019	0.0055	27	0.0007	0.9984	[35]
	AMB-FUBINACA (short)						0.9861	0.0024	0.0109	30	0.0009	0.9844	0.0024	0.0082	24	0.0010		
	ADB-CHMINACA	0.9910	0.0034	0.0089	11	0.0020	1.0005	0.0061	0.0113	3	0.0069	0.9984	0.0038	0.0075	3	0.0043		
	MDMB-CHMICA	0.9460	0.0009	0.0040	60	0.0002	0.9488	0.0020	0.0070	30	0.0007	0.9477	0.0013	0.0047	23	0.0005	0.9415	[35]
	MDMB-FUBINACA	0.9645	0.0014	0.0036	9	0.0009	0.9609	0.0005	0.0009	3	0.0005	0.9586	0.0007	0.0013	3	0.0008		

Table 4. A comparison of ITMS™ and GC-MS analysis results for seized paper samples (n=392).

Agreement between ITMS and GC-MS results	Instrument			
	Itemiser® 3E		Itemiser® 4DN	
	Count *	%	Count *	%
Agree	358	91.1	365	92.9
-ve ITMS™ / +ve GC-MS	13	3.3	10	2.6
+ve ITMS™ / -ve GC-MS	21	5.4	18	4.6
Likely cross-contamination	12	3.1	11	2.8
Other	9	2.3	7	1.8

* Of a total of 392 seized paper samples.

Table 5. Itemiser® 3E and 4DN results for all prison samples in comparison to the GC-MS result. There are only 392 samples, but 407 alarms for the 3E because 11 samples had two different alarms, 1 sample had three different alarms, and 2 samples were run on two different 3E instruments with different alarm results. There are 416 alarms for the 4DN because 23 samples had two different alarms and 1 sample was run on both 4DN instruments with different alarm results.

Alarm	Itemiser® 3E						Itemiser® 4DN					
	Agreement with GC-MS?		Positive ITMS™ / Negative GC-MS	Negative ITMS™ / Positive GC-MS	Likely cross contamination	Total	Agreement with GC-MS?		Positive ITMS™ / Negative GC-MS	Negative ITMS™ / Positive GC-MS	Likely cross contamination	Total
	Yes Count (%)	No Count (%)					Yes Count (%)	No Count (%)				
No Alarm	183 (50.3%)	-	-	13 (100%)	-	196 (48.2%)	189 (51.2%)	-	-	10 (100%)	-	199 (47.8%)
Spice 2	-	1 (11.1%)	2 (22.2%)	-	-	3 (0.7%)	-	3 (16.7%)	-	-	-	3 (0.7%)
Spice 4	3 (0.8%)	1 (11.1%)	-	-	2 (16.7%)	6 (1.5%)	35 (9.5%)	3 (16.7%)	-	-	1 (9.1%)	39 (9.4%)
Spice 5	42 (11.5%)	-	-	-	1 (8.3%)	43 (10.6%)	3 (0.8%)	4 (22.2%)	-	-	-	7 (1.7%)
Spice 6	-	-	1 (11.1%)	-	-	1 (0.2%)	-	8 (44.4%)	1 (12.5%)	-	-	9 (2.2%)
Spice 8	46 (12.6%)	-	-	-	4 (33.3%)	50 (12.3%)	66 (17.9%)	-	2 (25.0%)	-	6 (54.5%)	74 (17.8%)
Spice 9	81 (22.3%)	-	3 (33.3%)	-	5 (41.7%)	89 (21.9%)	72 (19.5%)	-	2 (25.0%)	-	4 (36.4%)	78 (18.8%)
Sub-Total	**355**	**2**	**6**	**13**	**12**	**388**	**365**	**18**	**5**	**10**	**11**	**409**
Buprenorphine+	-	1 (11.1%)	3 (33.3%)	-	-	4 (1.0%)	-	-	-	-	-	-
Cocaine	8 (2.2%)	1 (11.1%)	-	-	-	9 (2.2%)	4 (1.1%)	-	3 (37.5%)	-	-	7 (1.7%)
Gabapentin+	1 (0.3%)	-	-	-	-	1 (0.2%)	-	-	-	-	-	-
Street Heroin+	-	2 (22.2%)	-	-	-	2 (0.5%)	-	-	-	-	-	-
Tramadol+	-	3 (33.3%)	-	-	-	3 (0.7%)	-	-	-	-	-	-
Total (all)	**364 (100%)**	**9 (100%)**	**9 (100%)**	**13 (100%)**	**12 (100%)**	**407 (100%)**	**369 (100%)**	**18 (100%)**	**8 (100%)**	**10 (100%)**	**11 (100%)**	**416 (100%)**

Core	Link	Tail	Linked Group	SCRA Name
γ-carboline	Methyl	5-fluoropentyl	CUMYL	5F-Cumyl-Pegaclone (7)
Indazole	Carboxamide	4-cyanobutyl		Cumyl-4CN-BINACA (5)
		4-fluorobutyl	MDMB	4F-MDMB-BINACA (2)
		5-fluoropentyl	ADB	5F-ADB-PINACA (11)
			AMB	5F-AMB-PINACA (12)
			MDMB	5F-MDMB-PINACA (4)
		Cyclohexylmethyl	AB	AB-CHMINACA (14)
		Fluorobenzyl	AB	AB-FUBINACA (19)
			ADB	ADB-FUBINACA (8)
			AMB	AMB-FUBINACA (15)
			EMB	EMB-FUBINACA (13)
			MDMB	MDMB-FUBINACA (18)
		Pent-4-enyl	MDMB	MDMB-4en-PINACA (3)
Indole	Carboxamide	5-fluoropentyl	MDMB	5F-MDMB-PICA (1)
		Cyclobutylmethyl	AMB	AMB-CHMICA (6)
			MDMB	MDMB-CHMICA (21)
		Pent-4-enyl	AMB	AMB-4en-PICA (16)
			MDMB	MDMB-4en-PICA (17)
	Carboxylate	5-fluoropentyl	Quinolinyl	5F-PB-22 (20)
		Fluorobenzyl		FUB-PB-22 (10)
		Pentyl		PB-22 (9)

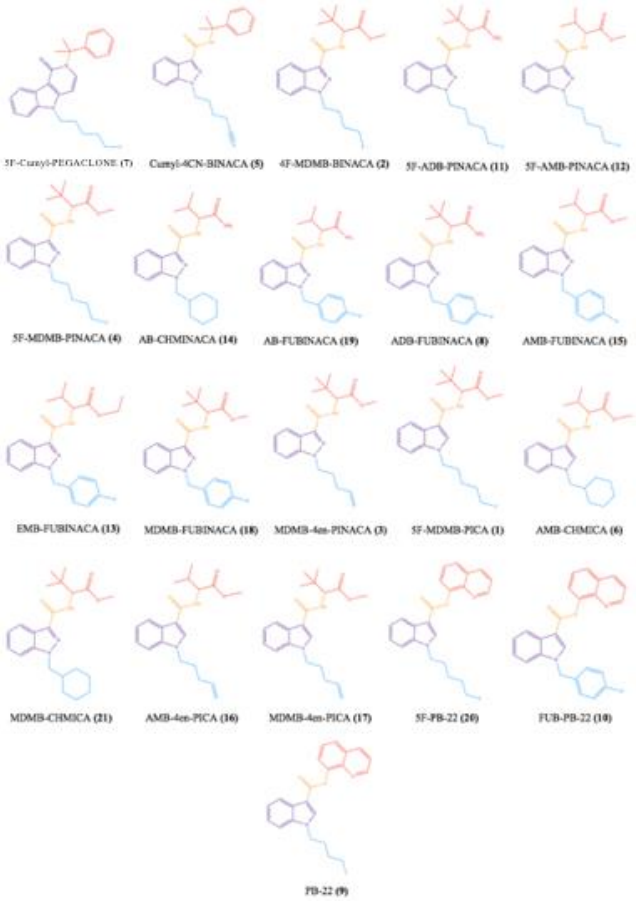

Figure 1. Structures of the synthetic cannabinoids analysed in this study.

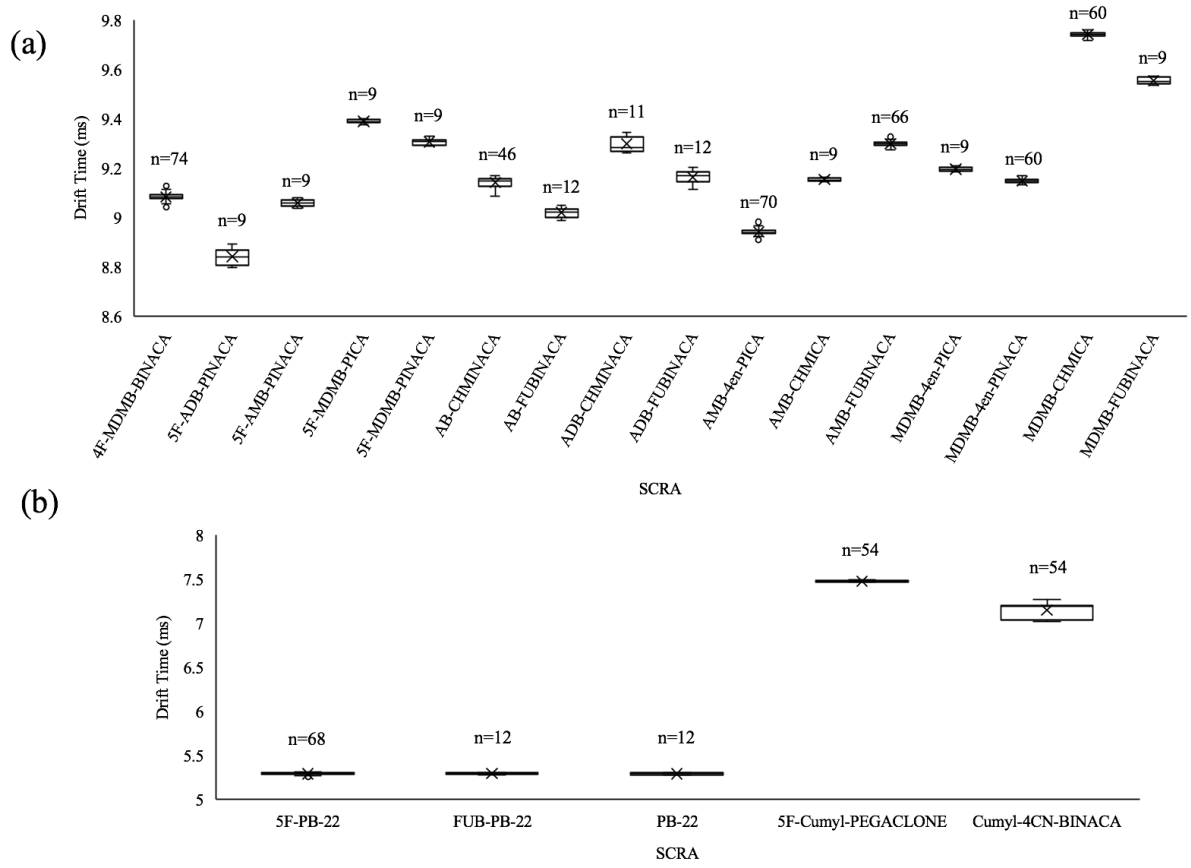

Figure 2. Drift time variation of SCRA data on Itemiser® 3E for (a) valinate- and tert-leucinate- indazole- and indole-3-carboxamide SCRAs and (b) cumyl and quinolinyl compounds.

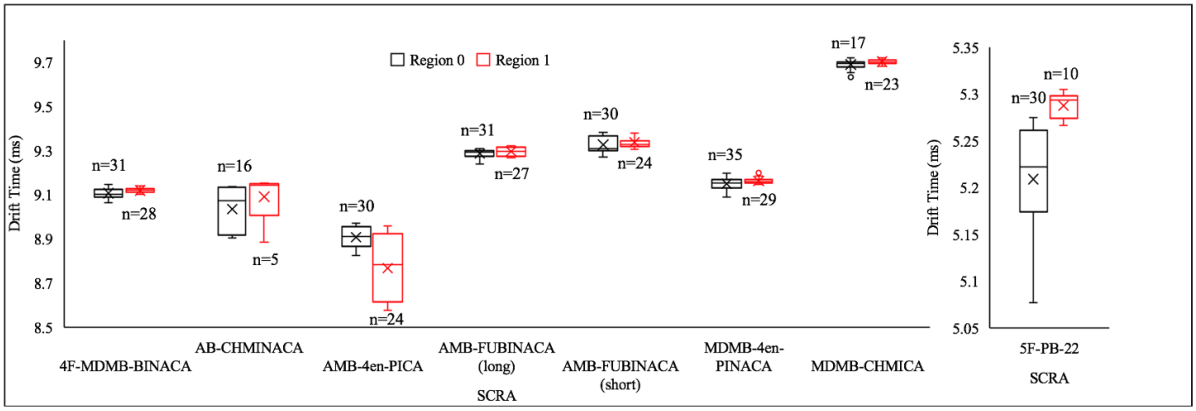

Figure 3. Drift time variation of SCRA data on the Itemiser® 4DN ITMS systems. The Itemiser® 4DN provides two datasets for each sample, which are differentiated in the figure as Region 0 (black) and Region 1 (red). 12 additional SCRAs were tested, but since there were only three replicate analyses of each SCRA, they are not included in this figure; however, their data can be found in Table 2.

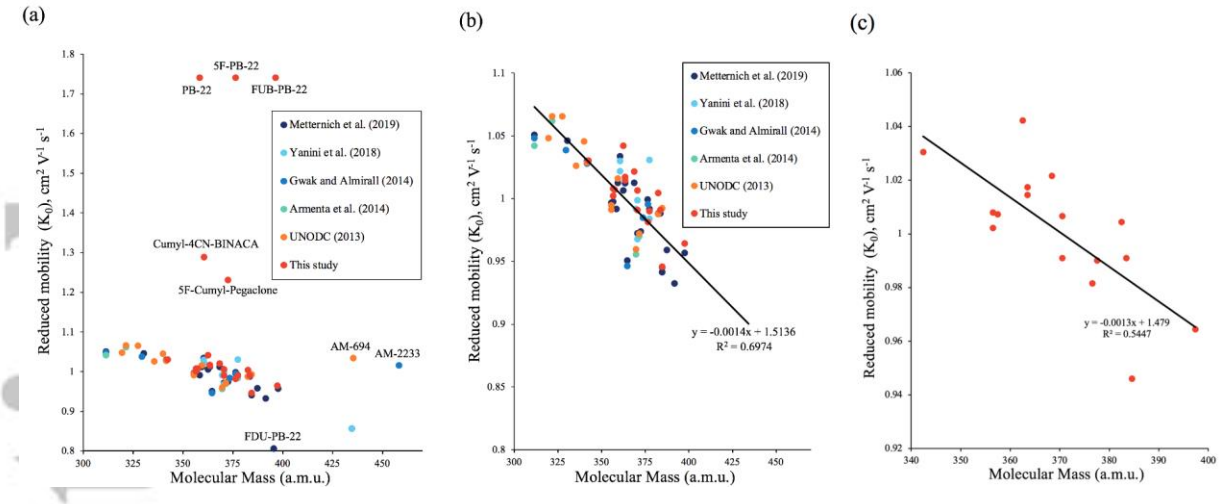

Figure 4. The relationship between reduced mobility and molecular mass (a) all available SCRA data from this and published studies, (b) selected SCRA data from this and published studies, and (c) leucinate and valinate indazole- and indole-3-carboxamide SCRA data from this study.

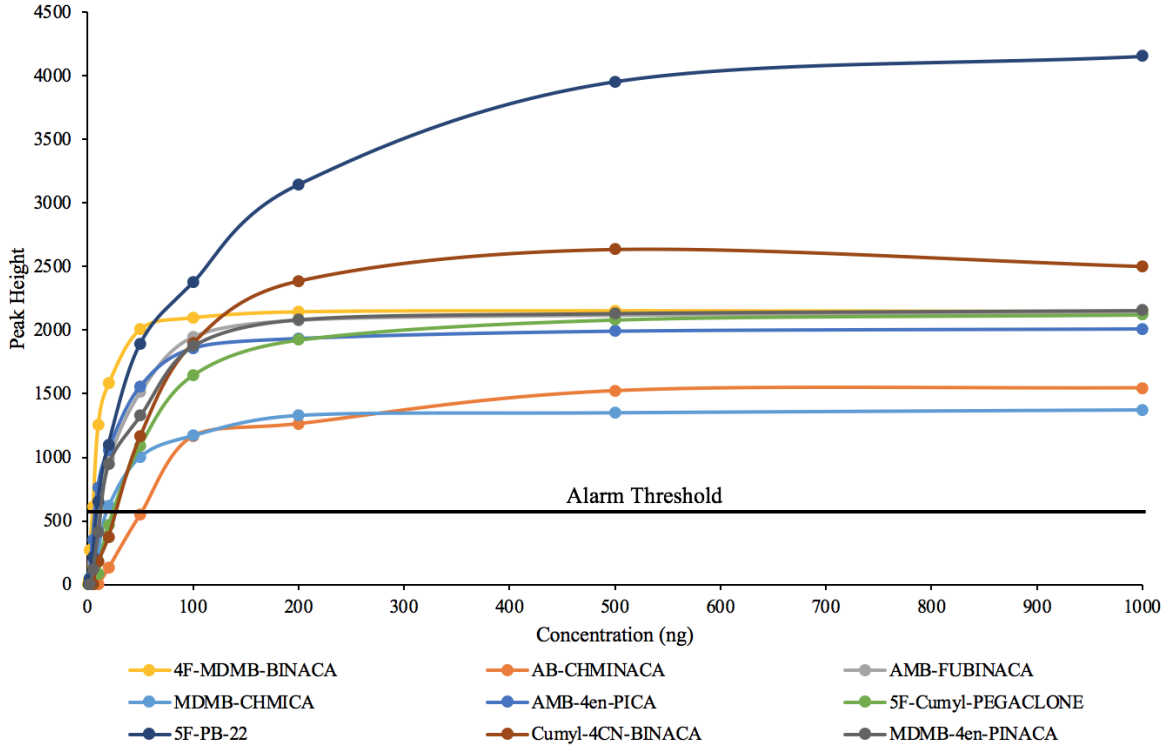

Figure 5. Relationship between synthetic cannabinoid receptor agonist sample trap loading mass (ng) and mean detector response for three Itemiser® 3E instruments. A line for the average alarm threshold is included at a peak height of 500. Lines provided linking data are point to point, are shown for illustrative purposes and have no statistical meaning.

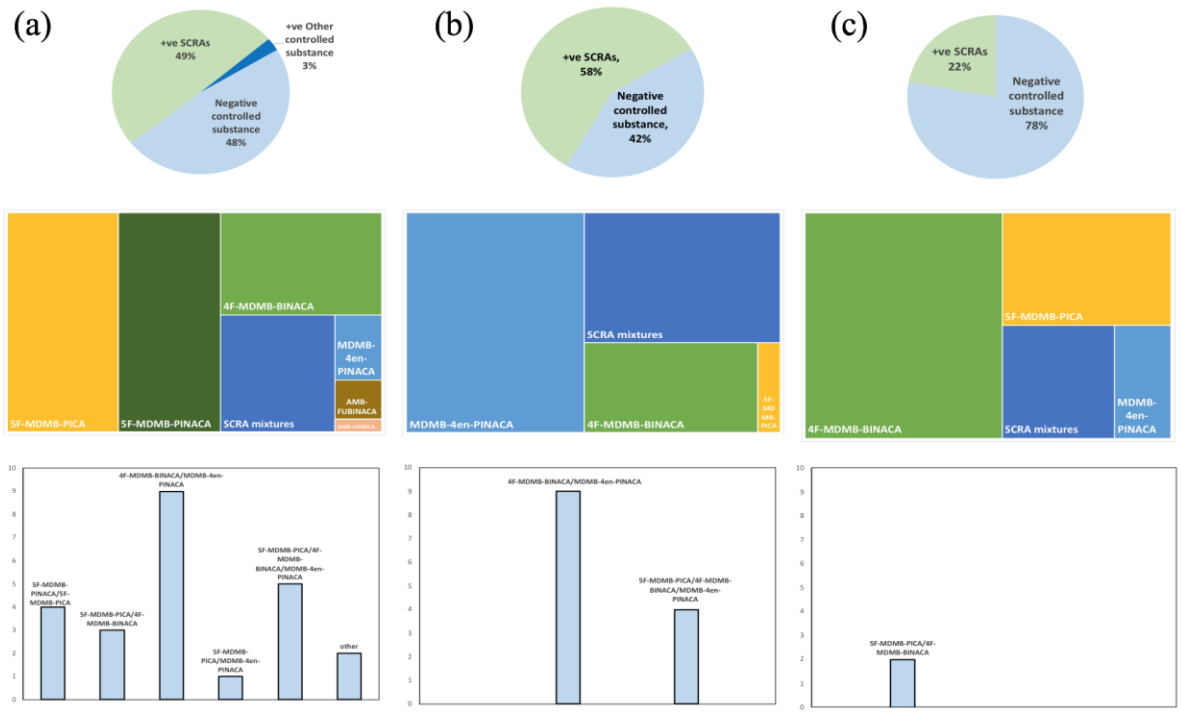

Figure 6. Summary of qualitative gas-chromatography mass spectrometry data for the SCRAs in infused papers from Scottish prisons (a) from prisons 1-3 between June 2018 and September 2019 as previously reported by Norman et al., 20206, (b) from prison 1 September 2019 to 20th December 2019 and (c) from prison 4. Sample information for samples shown in (b) and (c) can be found in the supplementary information Table S1.

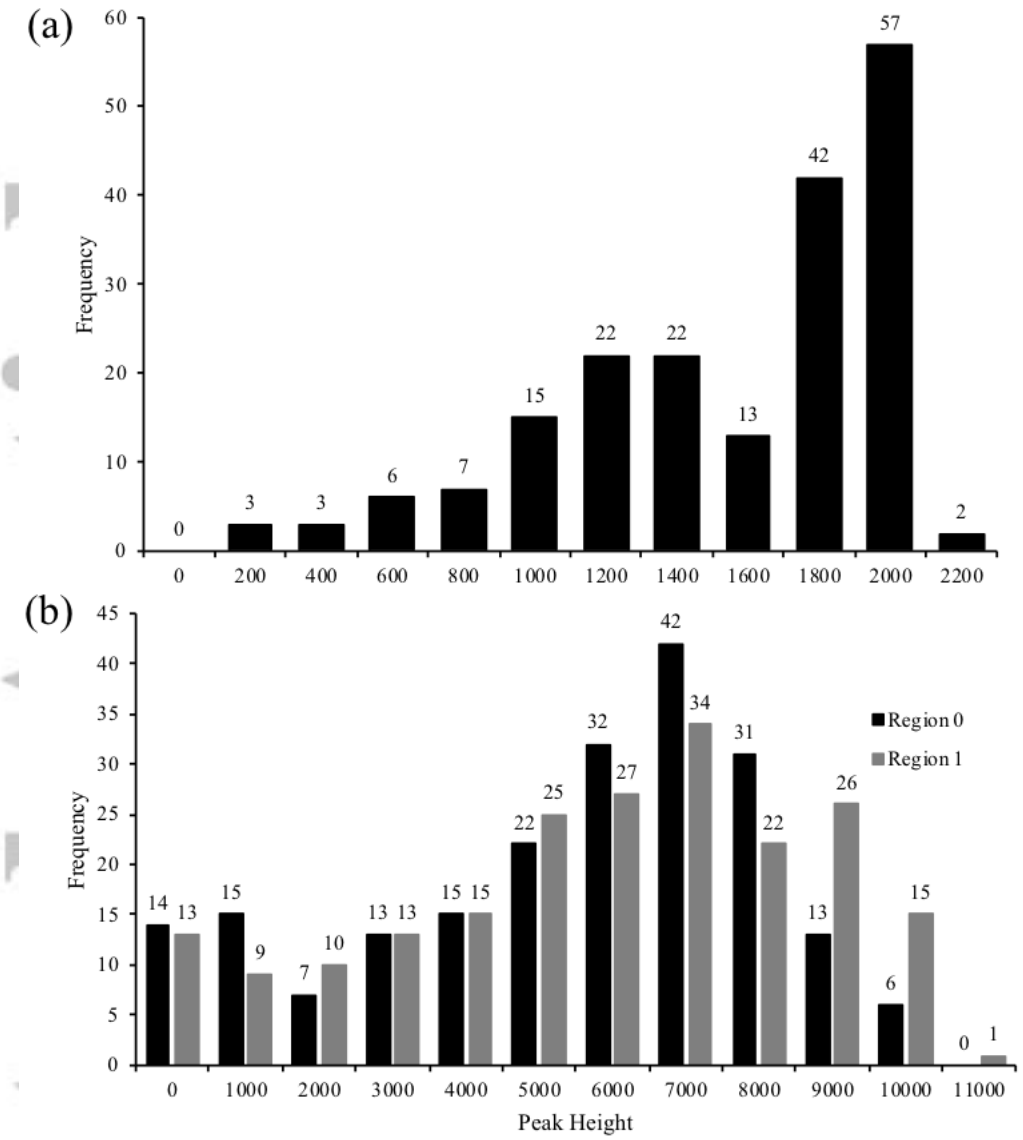

Figure 7. Frequency of analyte peak height for all SCRA alarms for the prison samples on (a) the Itemiser® 3E (n = 192) and (b) the Itemiser ® 4DN by detection region (Region 0 (black), Region 1 (red), n = 210).

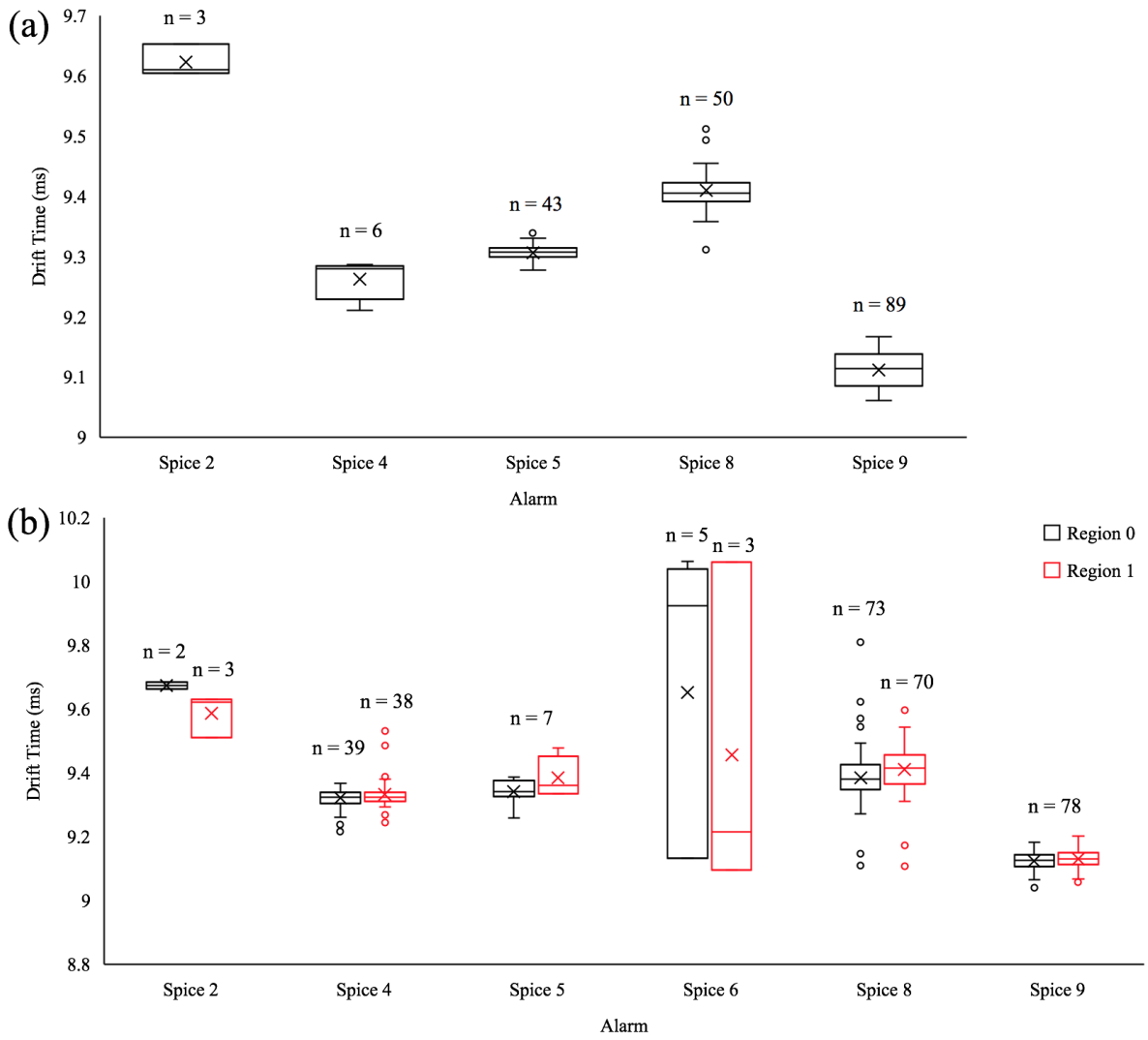

Figure 8. Drift time variability of all SCRA alarms for the prison samples on the (a) Itemiser® 3E (n = 191) and (b) the Itemiser® 4DN by detection region: Region 0 (black, n = 204) and Region 1 (red, n=199).

The applicability of benchtop Ion Mobility Spectroscopy (IMS) instruments for the detection of synthetic cannabinoid receptor agonists (SCRAs) in prisons in an evolving illicit market is assessed by the analysis of 401 seized paper samples suspected to be infused with SCRAs.

Large-scale evaluation of ion mobility spectrometry for the rapid detection of synthetic cannabinoid receptor agonists in infused papers in prisons

Caitlyn Norman, Brian McKirdy, Gillian Walker, Pat Dugard, Niamh Nic Daéid, Craig McKenzie*